

Remarks

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Thus, in response to the rejection of claim 11 under the second paragraph of 35 U.S.C. §112, this claim has been amended to delete the specific (i.e. "including"), embodiments, rendering the rejection moot.

Accordingly, new claim 12 has been added to the application, directed to the specific embodiments deleted from claim 11.

New claims 13-16 have also been added to the application, directed to the amounts of saccharide compound in the formulation. Claims 13-15 are supported by page 3, lines 20-22 of the specification; and claim 16, which requires that the formulation does not contain a saccharide compound, is supported by page 2, lines 9-10, as well as Examples 1 and 2, for formulations which do not contain any saccharide compound.

The patentability of the presently claimed invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Thus, the rejection of claims 1-11 under 35 U.S.C. §103(a) as being unpatentable over Harris et al. (US '450) in view of Daniel et al. (WO '560) is respectfully traversed.

The Examiner submits that Harris et al. teach a composition comprising

- the compound of formula I in claim 1 of the instant invention,
- component b (alkali or alkaline earth metal carbonate), and
- a saccharide compound.

The Examiner concedes that Harris et al. do not teach or make provision that the formulation does not contain a substantial amount of a saccharide compound. However, the Examiner submits that the wt% range of saccharide of Harris et al. is 1% to about 90%, preferably about 10% to about 80%, referring to the disclosure at column 3, lines 56-58 of this reference.

However, the percentages referred to by the Examiner, i.e. 1% to about 90%, preferably about 10% to about 80% do **not** appear at column 3, lines 56-58 referred to by the Examiner, but rather, appear at column 3, lines 40-42, which disclose the quantity of

“the stabilizer component”, i.e. the “alkaline stabilizer” (column 3, line 28). The quantity of the saccharide, set forth at column 3, lines 56-58, is from about 5% to about 90%, preferably about 10% to about 80%. **Thus, in the context the broadest generic disclosure in Harris et al., the minimum amount of saccharide in the composition is about 5%, which is substantially greater than the amount of less than 2% in new claim 15 set forth above, and of course, also does not suggest the formulation of new claim 16, which does not contain a saccharide compound.** In this regard, it is evident from reading Harris et al. that it is an **essential** feature of their invention to use a saccharide together with an alkaline stabilizer. See, e.g., the Abstract, “The Invention” section, and claim 1 (feature c)).

From the text and working examples of this reference, it is clear that Harris et al. teach the incorporation of a substantial amount of a saccharide compound and direct the skilled person **away from** not using a saccharide. The amount of saccharide in Harris et al.’s disclosed examples is **38%** (Example A), **15.3%** (Example B), and **78.5%** (Example C). Example C is a comparative example without an alkaline stabilizer (magnesium carbonate is used in other examples as an alkaline stabilizer). Example D in Harris et al. is a comparative example where a saccharide is not used, and magnesium carbonate is used as the alkaline stabilizer. Example D results in unacceptably high degradation.

Consequently, Harris et al. teach that stable formulations are obtained using a saccharide and an alkaline stabilizer, in particular magnesium carbonate.

The problem that the instant invention can be seen as addressing having regard to the state of the art at the time of the invention, is how to provide an alternative stable formulation, which does not include a substantial amount of a saccharide compound, e.g. less than 10% of a saccharide compound (new claim 13).

This problem is addressed by the instant invention by providing a formulation comprising:

- a) the active ingredient (as defined in claim 1),
- b) an alkali or alkaline earth metal carbonate,
- c) an insoluble alkaline-earth metal salt of hydrogen phosphate, and
- d) no substantial amount of a saccharide compound.

Harris et al. deviate from the instant invention in two respects, they teach the use of a substantial amount of saccharide, and do not teach use of an insoluble alkaline-earth metal salt of hydrogen phosphate, i.e. the reference lacks both features c) and d) of the instant invention.

Daniel et al. teach that formulations of ACE inhibitors can be stabilized with the use of magnesium oxide as a stabilizing agent and a suitable amount of a “hydrolysis-minimizing” agent. This appears clearly in claim 1 of Daniel et al. where magnesium oxide is defined as the stabilizer component (b), and on page 3, lines 13-15, from which it is learned that the gist of Daniel et al.’s invention is to use magnesium oxide instead of magnesium carbonate hydroxide, as a primary cyclization stabilizer.

It is correct that dicalcium phosphate is listed as a possible hydrolysis-minimizing agent, in a group of broadly defined compounds ("saccharides such as mannitol, lactose, and other sugars, diuretics, dicalcium phosphate, hydrochloro thiazide, and known fillers that have a hydrolysis-minimizing effect", see page 9, lines 11-14). However, saccharides are said to be most preferred (page 9, line 14), and in fact **all exemplified compositions contain saccharide, in the range from 16.7% to about 80%.**

Consequently, the composition taught by Daniel et al. is different than both the claimed compositions of the present invention and the compositions of Harris et al., in that Daniel et al.’s composition contains magnesium oxide and **not** an alkali or alkaline earth metal carbonate. In fact, Daniel et al. teach away from using alkaline earth metal carbonates; the text of page 16, lines 3-10, and page 17 “Results” section discusses that magnesium carbonate hydroxide is not at all as suitable as magnesium oxide.

Therefore, Applicant respectfully submits that it would not have been obvious for the skilled person to modify the teachings of Harris et al. in light of Daniel et al. In order to modify Harris et al. to arrive at the instant invention, the skilled person has to

- (i) depart from using a substantial amount of saccharide, which is an **essential** feature of the Harris et al. invention, and
- (ii) use an insoluble alkaline-earth metal salt of hydrogen phosphate.

It is not at all evident, let alone obvious, from reading the documents of Harris et al. and Daniel et al., that the two teachings can be combined to arrive at the present invention, as submitted by Examiner. Harris et al. quite clearly teach compositions with a

substantial amount of saccharides and that they are beneficial over other compositions of ACE inhibitors as discussed above. Daniel et al. also disclose compositions that contain saccharides and do in fact not exemplify any compositions without a saccharide, and further **teach away** from using an alkali or alkaline earth metal carbonate as mentioned above. Only in hindsight could it appear obvious to combine the teachings of Harris et al. and Daniel et al. to arrive at a composition which:

1. comprises a less than substantial amount of saccharide (used in all exemplified compositions of Harris et al. and Daniel et al. and an essential feature of Harris et al., which teach away from not using a saccharide);
2. comprises an alkali or alkaline earth metal carbonate, which Daniel et al. do not include and in fact teach away from, as they direct the skilled person to use magnesium oxide; and
3. comprises an insoluble alkaline-earth metal salt of hydrogen phosphate, not exemplified in either prior art document and only listed by Daniel et al. in a list of many untried compounds as a potential ingredient in magnesium oxide-containing compositions.

With particular regard to the second point above, Applicant notes that both the Harris et al. reference and the Daniel et al. reference are owned by Warner-Lambert Company, and that page 1, line 17 of Daniel et al. cites its own Harris et al. reference as disclosing magnesium carbonate as a preferred stabilizer. As indicated above, the Daniel et al. reference specifically teaches the art-skilled to use magnesium **oxide** instead of magnesium carbonate. As the Examiner knows, the prior art must be considered from the standpoint of what it collectively fairly shows to one of ordinary skill in the art. In this light, taking the two references together, it must be fairly said that they teach using magnesium oxide, instead of magnesium carbonate, to prepare compositions containing ACE inhibitors. Accordingly, the formulation of the present invention, which must contain an alkaline earth metal carbonate, is not obvious from the references.

Earlier prior art relating to compositions of ACE inhibitors of the type discussed herein also clearly direct the skilled person to the use of a substantial amount of saccharides, as discussed in the Background section of the present application, and a

substantial amount of saccharide is used in the industry standard Accupril formulation, as mentioned by the Examiner.

Based on the above, Applicant submits that at the time of the invention there existed a consensus in the field that a substantial amount of saccharide was essential as a hydrolysis-minimizing compound in compositions with ACE inhibitors of the type which are discussed here, and in fact it can even be concluded that there was a prejudice against using less than a substantial amount of saccharide compounds.

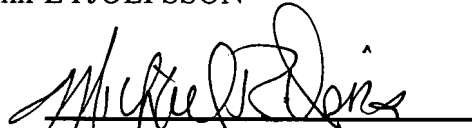
For these reasons, Applicant takes the position that the presently claimed invention is clearly patentable over the applied references.

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

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